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20792 7590 02/17/2004
MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER

GUZO, DAVID

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 02/17/2004

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/895,940	06/29/2001	Joseph S. Orlando	9151-16	9425

TITLE OF INVENTION: ADENOVIRUS E4 PROTEIN VARIANTS FOR VIRUS PRODUCTION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	\$665	\$300	\$965	05/17/2004

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

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B. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

If the SMALL ENTITY is shown as NO:

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B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status.
See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail

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(703) 746-4000**

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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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20792 7590 02/17/2004

**MYERS BIGEL SIBLEY & SAJOVEC
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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/895,940	06/29/2001	Joseph S. Orlando	9151-16	9425
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TITLE OF INVENTION: ADENOVIRUS E4 PROTEIN VARIANTS FOR VIRUS PRODUCTION

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nonprovisional	YES	\$665	\$300	\$965	05/17/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
GUZO, DAVID	1636	435-235100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent); ☐ individual ☐ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:

- ☐ Issue Fee
- ☐ Publication Fee
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):

- ☐ A check in the amount of the fee(s) is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

Director for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature)

(Date)

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Alexandria, Virginia 22313-1450.

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20792	7590	02/17/2004	EXAMINER	
MYERS BIGEL SIBLEY & SAJOVEC PO BOX 37428 RALEIGH, NC 27627			GUZO, DAVID	
			ART UNIT	PAPER NUMBER
			1636	
DATE MAILED: 02/17/2004				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) system (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (703) 305-1383. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

Notice of Allowability	Application No.	Applicant(s)	
	09/895,940	ORLANDO ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to the amendment filed 11/10/03.
2. ☒ The allowed claim(s) is/are 4,6-14,16,21-26 and 28-34.
3. ☐ The drawings filed on _____ are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☐ All b) ☐ Some* c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☒ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - (a) ☒ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) ☐ hereto or 2) ☒ to Paper No./Mail Date 14. (*Petition under 37 CFR 1.84 only is required*).
 - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|---|---|
| 1. <input type="checkbox"/> Notice of References Cited (PTO-892) | 5. <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 6. <input checked="" type="checkbox"/> Interview Summary (PTO-413),
Paper No./Mail Date <u>1</u> . |
| 3. <input type="checkbox"/> Information Disclosure Statements (PTO-1449 or PTO/SB/08),
Paper No./Mail Date _____ | 7. <input checked="" type="checkbox"/> Examiner's Amendment/Comment |
| 4. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 8. <input type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| | 9. <input type="checkbox"/> Other _____. |

Examiner's Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Jarett K. Abramson on 1/29/04.

The application has been amended as follows:

In the **Specification**:

Replace the Brief Description of Figure 1 on page 6 with the following:

-- **Figure 1** (Parts A-B) shows a representation of the amphipathic arginine-faced α helix. Amino acids 239 through 255 of the E40rf6 protein were modeled as an α helix by constraining the C α carbons to a standard α helix. The side chains were allowed to adopt an energetically reasonable configuration using molecular dynamics as described in the **Example 1**. The identity of each atom is indicated by color: nitrogen = blue, carbon = gray, oxygen = red, sulfur = yellow. Hydrogen atoms are not shown. The lone pair of electrons associated with the sulfur is shown in green. Atoms in the peptide backbone are rendered in a muted color. The charged residues that are visible are labeled near the side chain. (A) View down the helix axis (N-terminus to C-terminus). (B) View of the hydrophilic face. --

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Replace the Brief Description of Figure 2 on page 6 with the following:

--**Figure 2** (Parts A-C) shows an E4orf6 variant bearing arginine to lysine substitutions within the amphipathic α helix retains the E1B-55 kDa protein in the nucleus after transfection. (A) The amino acid sequence of the amphipathic α helix (E4orf6 residues 239-255, SEQ ID NO:26) and a variant showing amphipathic α helix the arginine to lysine substitutions at positions 241, 243, 244 and 248 (R4K, SEQ ID NO: 27). (B) HeLa cells were infected with a recombinant vaccinia virus vTF7.3 to establish expression of the T7 RNA polymerase and then transfected with cDNA under control of the T7 promoter to express the E4orf6-related protein (left column) and the E1B-55 kDa protein (center column). The transfected cDNAs are identified on the left. Ad proteins were visualized by double-label immunofluorescence at 12 h after transfection and representative cells are shown. E4orf6 proteins were visualized with the mouse monoclonal antibody, MAb 3 (left column; α E4orf6), E1B-55 kDa protein was visualized with the rat monoclonal antibody, 9C10 (Zantema et al. (1985) *Virology* 142:44-58) (center column; α E1 B-55K) and DNA was visualized with DAPI (right column; DNA). (C). In parallel with the samples prepared for immunofluorescence, expression of the E4orf6 and E1B-55 kDa proteins was established by transfection of the cDNAs indicated above each lane. Total cell protein was isolated 12 h after infection-transfection, separated by SDS-PAGE and transferred to a solid support. The E4orf6-related proteins and the E1B-55 kDa protein were visualized by immunoblotting with MAb 3 (Marton et al. (1990) *J. Virol.* 64:2345-2359) and 2A6 (Salnow et al. (1982)

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Virology 120:510-517) respectively. Only the portion of the membranes containing the E4orf6-related proteins and the E1B-55 kDa proteins are shown. --

Replace the Brief Description of Figure 3 on page 7 with the following:

-- **Figure 3** (Parts A-E) shows the degree of E1B-55 kDa nuclear localization in cells expressing the R₂₄₀E variant varies from cell to cell. Expression of the R₂₄₀E E4orf6 variant and the E1B-55 kDa protein was established and the localization of the E1B-55 kDa protein determined as described in the legend to **Figure 2**. The E1B-55 kDa protein was visualized with the rat monoclonal antibody 9C10. The localization represented in (A) and (B) was seen in 55% of the cells and was scored as nuclear. The uniform distribution represented in (C) was seen in only 4% of the cells and the predominantly cytoplasmic localization seen in (D) and (E) was seen in 46% of the cells. The uniform and cytoplasmic distributions were scored as cytoplasmic. --

Replace the Brief Description of Figure 4 on page 7 with the following:

-- **Figure 4** (Parts A-B) shows E4orf6 variants with arginine to alanine replacement mutations at positions 241 or 243 do not retain the E1B-55 kDa protein in the cell nucleus after transfection. (A) Expression of the E4orf6-related proteins (indicated on the left) and the E1B-55 kDa protein was established, and the localization of the Ad proteins determined as described in the legend to Figure 2. Representative

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images of a single cell from each transfection are presented with the E4orf6 protein shown in the left column (α E4orf6), E1B-55 kDa protein in the center column (α E1B-55K), and DNA visualized with DAPI in the right column (DNA). (B) In parallel with the samples prepared for immunofluorescence, expression of the E4orf6 and E1B-55 kDa proteins was established by transfection of the cDNAs indicated above each lane and the E4orf6-related proteins and the E1B-55 kDa protein were visualized by immunoblotting as described in the legend to **Figure 2**. --

Replace the Brief Description of Figure 6 on page 8 with the following:

-- Figure 6 (Parts A-G) shows E4orf6 variants that interact with the E1B-55 kDa protein are positively charged at the amino terminus of the amphipathic α helix. Amino acids 239 through 255 of E4orf6 protein variants were modeled as an α helix by constraining the positions of the C α carbons to that of a standard α helix. The side chains were allowed to adopt an energetically reasonable configuration using molecular dynamics as described in the Methods. The solvent accessible surface of the model peptide was calculated and the electropositive potential of the molecule was projected onto this surface. The most electropositive regions are mapped to deep blue and the most negative regions mapped to bright red as indicated by the scale (kcal/mol e $^{-}$) (kilocalories per mole of electrons) on the right. The orientation of the α helical peptides is the same as seen in **Figure 1B** where the amino-terminus is at the top and the hydrophilic face is exposed. The models and associated value for nuclear E1B-55 kDa

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protein retention (from **Figure 5**) are (A) wild- type E4orf6 protein, 100%; (B) R₂₅₁A, 99%; (C) R₂₄₄E, 91%; (D) R_{248,251}A, 80%; (E) R₂₄₁A, 72%; (F) R_{240,244,251}A, 62%; (G) R₂₄₁E, 0.8%. --

Replace the Brief Description of Figure 7 on page 8 with the following:

-- Figure 7 (Parts A-B) shows the ability of the E4orf6 protein to retain the E1B-55 kDa protein to the nucleus is neither necessary nor sufficient to correct the growth defect of an E4- deletion virus. A "faster growing strain" of HeLa cells (**A**) and a "slower growing strain" of HeLa cells (**B**) were infected with an E4-deletion virus lacking all E4 open reading frames except orf4, *d1/1014*, or a phenotypically wild-type virus, *d1/309*, at 10 PFU per cell and simultaneously transfected with cDNAs expressing the E4orf6-related constructs listed below each graph. The E4orf6-related proteins were expressed under the control of the major immediate-early promoter of CMV. Progeny virus was harvested after 48 hrs and quantified by plaque assay on the E4-complementing W162 cell line (Weinberg and Ketner (1983) *Proc. Natl. Acad. Sci. USA* **80**:5383-5386). A representative experiment (of three) showing the average amount of virus (expressed as PFU per milliliter of initial culture volume) obtained from two independent infections is shown. The range of virus recovered in the two independent infections is indicated by the brackets on the right. --

Replace the Brief Description of Figure 10 on page 9 with the following:

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-- Figure 10 (Parts A-B) shows the expression of the wild-type E4orf6 protein cannot be sustained and is deleterious to HeLa cells but not REF-52 cells. HeLa cells and REF-52 cells were transfected with the E4orf6-related constructs indicated on the right of each graph and placed under selection according to the protocol described in **Figure 9**. The percent of cells expressing the E4orf6-related protein is shown as a function of time after transfection and selection. All non-transfected cells were killed within 14 days of selection. (A) HeLa cells tolerate stable expression of the non-functional E4orf6 variants (R₂₄₁P, L₂₄₅P, and E4orf6/7) but not the wild-type protein nor the functionally wild-type proline-variant, AE₂₅₅APE. After 27 days following transfection (indicated by the arrowhead), no cells remained in the samples transfected with the wild-type construct or the AE₂₅₅APE construct. (B) REF-52 cells tolerate stable expression of all E4orf6-related constructs. --

Replace the Brief Description of Figure 11 on page 10 with the following:

-- Figure 11 (Parts A-D) shows that the inability to form neomycin-resistant cell colonies reveals that E4orf6 [cytotoxicity] cytotoxicity is cell type-specific. The cells indicated on each panel were transfected with the indicated plasmids to express only the neomycin-resistance gene (vector) or the resistance gene and the non-functional proline-mutant (L₂₄₅P) or the wild-type E4orf6 protein (E4orf6). Two days after transfection, the cells were harvested and replated in triplicate at low cell density in the presence of 600 µg/ml G418. After 21 days, the number of neomycin-resistant colonies

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were counted and the values \pm SD plotted. Neomycin-resistant cell colonies could not be recovered from 293 cells transfected with the vector expressing the wild-type E4orf6 protein. This value is plotted as \square 1 in panel B. --

In the **Claims**:

8. (Currently Amended) The method according to claim 9, wherein said nucleic acid encoding said mutant adenovirus E4orf6 gene is carried by a plasmid[s], bacteriophage, cosmid or retrovirus.

9. (Currently Amended) A method of packaging a recombinant viral vector, comprising the steps of:

(a) providing a packaging cell, said packaging cell containing and expressing a nucleic acid encoding a mutant adenovirus E4orf6 protein, said E4orf6 protein containing at least one mutation in the region encoding amino acids 230 to 260 wherein said at least one mutation comprises a substitution mutation at position 240, 241, 243, 244, 248, or 251;

(b) transfecting or infecting said packaging cell with a nucleic acid that encodes a recombinant viral vector selected from the group consisting of adenovirus vectors and adeno- associated virus vectors, wherein said vector lacks a functional gene encoding E4orf6 protein; and wherein said mutation renders said mutant adenovirus E4orf6 protein non-toxic to said transfected cells;

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(c) culturing said transfected cells under conditions that permit expression of the mutant E4orf6 protein and the production of packaged recombinant viral vector therein; and then

(d) collecting packaged recombinant viral vector from said cultured cells.

The Sequence Listing filed 11/10/03 is acceptable and has been entered.

The drawings are objected to because a Petition under 37 CFR 1.84 is required for acceptance of color drawings. Applicants must comply with the requirements of 37 CFR 1.84(a)(2)(i)-(iv) for acceptance of color drawings and 37 CFR 1.84(b)(2) for color photographs. Otherwise, the drawings are approved by the examiner.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
January 29, 2004


DAVID GUZO
PRIMARY EXAMINER